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Original Article

Serum Prolactin Level after Febrile Seizure versus Epileptic Seizure in 6-Month-Old to 5-Year-Old Children

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Abstract

Background: Serum prolactin level has been used as an alternative determinant to help differentiate epileptic from non-epileptic seizures. We aimed to analyze the association between serum prolactin concentration and epileptic seizure versus febrile seizure as well as seizure duration, single versus multiple seizure attacks and time lapse between seizure onset and blood sampling.

Methods: Seventy patients aged 6 months to 5 years with seizure who admitted to the emergency department between March 2004 and February 2005 were selected and divided into group I (epileptic seizure) and group II (febrile seizure). Group III consisted of 35 pediatric patients without seizure. Blood samples were collected within 2 hours after seizure. Serum prolactin levels were measured, and statistical analyses were performed to detect possible associations between variables.

Results: Serum prolactin level increased about twice the normal level after epileptic seizures but not after febrile seizures or in the control group. The length of seizure and multiple seizure attacks were positively associated, whereas the lapse between seizure onset and blood drawing was negatively correlated with an increase in serum prolactin level.

Conclusion: Febrile (non-epileptic) seizures were not associated with increased serum prolactin level. Elevated prolactin level within 2 hours of a seizure may be suggestive of epileptic origin of the seizure.

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Keywords ● Prolactin ● febrile seizures ● epileptic seizures

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Introduction

Up to 5% of children aged 6 months to 5 years experience at least one episode of febrile seizure, broadly defined as simple or complex.[1] After an initial febrile seizure, about 3-12% of children will subsequently develop epilepsy. The risk of developing epilepsy after a simple febrile seizure is low (1.5–2.4%).[2] On the other hand, many children with seizures (such as children with febrile seizure) do not have epileptic seizures, and therefore do not need further investigation or treatment.[3] Jeavons and co-workers showed that 20% of patients treated as having epilepsy did not actually have the disease.[3] The co-existence of pseudoseizures with

epilepsy is as high as 33%.[4]

The adverse effects of anticonvulsant drugs, the duration and expense of treatment, and social implications make accurate diagnosis of the disease essential before starting treatment. Electroencephalographic findings may be normal, non-pathognomic, or inconclusive.[5] In developed countries, expensive, sophisticated, and time-consuming investigations such as 24-hour video EEG-monitoring, ambulatory EEG, provocative EEG tests, and single photon emission computed tomography (SPECT) are used in cases of diagnostic uncertainty; however, many of these techniques are not easily available in many developing countries, hence a cheaper and more easily accessible alternative is required.[5]

Prolactin release from the pituitary is controlled by the hypothalamus via a prolactin inhibitory factor now believed to be dopamine.[6] It is presumed that during generalized tonic-clonic seizure and most complex partial seizures, which originate in the temporal lobe, the spread of electrical activity from the ventromedial hypothalamus and medial temporal structures leads to release of a specific prolactin regulator into the hypophyseal portal system and consequently an increase in prolactin.[7-11] Thereafter, there is a progressive decline in prolactin release because of diminished electrical discharges and depletion of prolactin storage. In febrile seizures, subclinical electrical activity does not exist and after discharges are less intense and too brief to affect the ventromedial hypothalamus or lead to a rise in prolactin level.[11] Therefore, elevated serum prolactin level may be helpful in distinguishing epileptic seizures from non-epileptic convulsions (such as febrile seizure) or other non-epileptic paroxysmal events.[5,12-17] However, some researchers have questioned the validity of serum prolactin level in differentiating between febrile (non-epileptic) and epileptic seizures.[13] We aimed to determine whether serum prolactin level could be used to differentiate epileptic from febrile seizure, and to correlate hormone levels with seizure duration, repetitive seizures and the lapse between seizure onset and blood sampling.

Patients and Methods

This prospective study was performed between March 2004 and February 2005. We enrolled 105 children and after taking a detailed history and performing physical examination divided them into three groups. The patients were 6 months to 5 years old, and 70 of them had seizure attacks with or without fever. They were admitted to the emergency department of Motahary Teaching Hospital, affiliated to Urmia University of Medical Sciences, within 2 hours after a seizure attack. Exclusion criteria were any metabolic disturbance, infective central nervous system pathology, developmental, structural, or neurological abnormalities, or consumption of drugs known to alter prolactin levels. Group I consisted of 35 patients with epileptic seizures. Group II included 35 patients with febrile seizure. The control group (group III) consisted of 35 children admitted for reasons other than fever or seizures, and who did not have any disease or medication use that could alter their prolactin level. Informed consent was obtained from the parents.

Two milliliters of blood were collected on admission. The time lapse between the event and blood collection was recorded. Serum prolactin levels were quantitatively assessed with ELISA method. Hormone levels were considered elevated if the values were greater than 23 ng/ml, which is the upper limit of normal for all age groups and both sexes. The serum prolactin level in each group was plotted against seizure type (generalized tonic-clonic versus other types), seizure duration, single or multiple seizure attacks and the time lapse between the seizure attack and blood sampling.

Statistical analysis was performed using SPSS version 12 software. To verify normal distribution of the data, we used the Kolmogorov-Smirnov test. To compare serum prolactin levels between the three groups we used analysis of variance and Tukey's test. To determine the relationships between serum prolactin level and the type of seizure, single versus multiple seizure attacks and time lapse between the seizure and blood sampling, we used Spearman's rho test.

Results

Mean age in groups I, II and III were 26 ± 9, 22 ± 11, and 25 ± 10 months, respectively. There were 19 boys and 16 girls in group I, 17 boys and 18 girls in group II, and 18 boys and 17 girls in group III. Differences in mean age, male to female ratio, and average time lapse between seizure attack and blood sampling did not differ significantly among the three groups. Post-ictal serum prolactin levels were significantly higher in group I (mean: 47.42 ng/ml, range: 37.92 – 56.63 ng/ml) compared with group II (mean: 18.78 ng/ml, range: 17.47 – 19.29 ng/ml), and group III (mean: 13.16 ng/ml, range: 11.85 – 15.26 ng/ml; $P<0.01$, table 1). Thirty patients (85.7%) in group I, 16 patients (45.7%) in group II, and five patients (14.2%) in

the control group had serum prolactin levels greater than 23 ng/ml. A definite correlation was seen between post-ictal serum prolactin level and seizure duration in the group I (r = 0.937, P = 0.01, table 2). Furthermore, in group I, mean serum prolactin values were significantly higher in generalized tonic-clonic seizures (mean 49.62 ng/ml, range 43.17 – 56.07 ng/ml) compared with the other types of seizure (mean 36.95, range 25.17 – 47.71 ng/ml). There was a significant direct linear relationship between multiple (repetitive) seizure attacks and serum prolactin level in group I (r = 0.24, P = 0.04, table 2). There was an inverse correlation between seizure and time lapse between the seizure and blood sampling (r = -0.955, P = 0.01, table 2). There was no correlation between seizure type and time lapse between the seizure and blood sampling.

Table 1: Post-ictal serum prolactin levels in patients with febrile seizure, epileptic seizure and the controls.

Groups	Serum prolactin level (ng/ml)	Range
I / Epileptic seizure	47.42	37.92 - 56.63
II / Febrile seizure	18.78	17.47 - 19.29
III / Control	13.16	11.85 - 15.26

Table 2: Correlation between serum prolactin level, and seizure duration, repetitive seizure, and time lapse between the event and blood sampling.

Results	Correlation coefficient (r)	P value	Correlation
Seizure duration	0.937	0.01	Direct
Seizure frequency	0.24	0.04	Direct
Time lapse	-0.955	0.01	Inverse

Discussion

Distinguishing between epileptic and non-epileptic seizures may be difficult. Our findings showed that post-ictal serum prolactin levels were significantly higher in patients with epilepsy.

Dirik and co-workers measured post-ictal serum prolactin and cortisol levels in 37 children with epilepsy, febrile seizure, or syncopal attack and in 37 normal controls. They found a significantly higher serum prolactin levels in the group with epilepsy.[17]

Shah and colleagues analyzed the effects of different types of seizure and non-epileptic events as well as the effects of seizure duration and time lapse between the time of seizure and blood sampling on serum prolactin level.[18] Most of their patients had serum prolactin levels above the upper normal limit (>18.1 ng/ml) after a simple partial seizure, complex partial seizure, or complex partial seizure with secondary generalization.

An inverse correlation between seizure and time lapse between the seizure event and blood sampling has been reported.[18] Studies have shown that elevated serum prolactin level is highly predictive of generalized tonic-clonic seizure or complex partial seizure. Serum prolactin, when measured in the appropriate clinical setting within 10 to 20 min after a suspected event, is a useful adjunct for distinguishing generalized tonic-clonic seizure or complex partial seizure from non-epileptic seizures in adults and older children.[14]

Conclusion

Our findings suggest that serum prolactin concentration increases after an epileptic seizure; however, it does not increase after a febrile seizure. We found an inverse correlation between seizure and time lapse to blood sampling in patients with epileptic seizures. Post-ictal prolactin elevation may be useful as a positive prognostic risk factor in children with seizures. Because we observed an inverse correlation between elevated serum prolactin levels and the time lapse between seizure and blood sampling, a blood sample should be obtained as soon as possible after the event.

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Conflict of Interest: None declared

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